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Prevalence of Contact Allergy to *p*-Phenylenediamine in the European General Population

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Population-based studies on contact allergy to *p*-phenylenediamine (PPD) are scarce. A cross-sectional study was performed to assess the prevalence of contact allergy to PPD and its risk factors in the general population of 5 European countries. A total of 10,425 subjects were interviewed, and a random sample (n = 2,739) was patch tested to PPD. Overall, 5,286 individuals (50.9%) reported having used hair colorants at least once in their lifetime (78% female, 20% male), and 35% had used hair colorants during the last 12 months. Hair colorant avoidance because of any skin problem during the lifetime was reported by 6%. Black henna tattoos had been used by 5.5% during their lifetime. The prevalence of PPD contact allergy was 0.8% (95% confidence interval 0.6–1.0%), with no statistically significant association with gender or hair dye use. The prevalence of PPD in black henna tattoo users was 3.2% versus 0.6% in nonusers ($P < 0.001$). A clinically relevant positive patch test reaction to PPD related to hair coloring products was found in 0.1% (95% confidence interval 0.0–0.2%). A significant association with PPD contact allergy was observed for subjects who had black henna tattoos in their lifetime, with an age- and gender-adjusted odds ratio of 9.33 (95% confidence interval 3.45–25.26, $P < 0.001$). Black henna tattoos are an important risk factor for PPD contact allergy.

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INTRODUCTION

The diagnosis of contact allergy is based on patch testing. However, a positive patch test reaction only indicates that an individual is sensitized and is not necessarily an indicator of allergic contact dermatitis. Allergic contact dermatitis occurs when exposure to an allergen exceeds the individual's threshold for elicitation.

Most studies on contact allergy are based on patch testing of consecutive eczema patients. *p*-Phenylenediamine (PPD), used as an indicator of allergy to hair coloring products, has been present in the baseline series for many years. Data on PPD allergy in this highly selected population have been extensively published (Krasteva et al., 2009; Thyssen and White, 2008; Thyssen et al., 2009), and the weighted prevalence average was found to be 4% in Europe (Thyssen and White, 2008).

Data on the prevalence of contact allergy to PPD in the general population are scarce. The data are generally derived from small studies conducted in a single country. The rates reported in those studies vary from 0% to 1.5% in Europe (Dotterud and Smith-Sivertsen, 2007; Mortz et al., 2001; Nielsen and Menné, 1992; Nielsen et al., 2001; Schäfer et al., 2001; Seidenari et al., 1990; Thyssen et al., 2009). The clinical relevance of PPD allergy to hair coloring products or black henna tattoos was not investigated in any of those studies. The objectives of this study were to obtain descriptive indicators in the European general population of the prevalence of contact allergy to PPD in users and nonusers of hair coloring products and to define the risk factors for PPD contact allergy.

RESULTS

Sociodemographic characteristics of hair colorant ever-users and nonusers

Overall 5,282 individuals (50.9%) reported that they had used hair coloring products (18.5% male, 81.4% female) at least once in their lifetime. The demographic characteristics of hair coloring products ever-users and nonusers are presented in Table 1. Other than gender distribution, the other demographic characteristics did not differ substantially between ever-users and nonusers. Similar distributions of smoking habits and body mass index were observed overall and in all countries. With regard to smoking habits and body mass index categories in strata of gender, data of hair dye users in the European Dermato-Epidemiology Network (EDEN) Study were comparable with those of the general

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Abbreviations: CI, confidence interval; EDEN, European Dermato-Epidemiology Network; IVDK, Information Network of Departments of Dermatology; OR, odds ratio; PPD, p-phenylenediamine

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Table 1. Sociodemographic characteristics of ever-users and nonusers of hair coloring products

	Total (N = 10,388)[1]			
	Not users (N = 5,100)		*Hair dye users (N = 5,282)*	
	N	%	N	%
Gender				
Men	3,887	76.2	980	18.5
Women	1,213	23.8	4,302	81.4
Age, y				
18–30	1,394	27.3	1,609	30.4
31–45	1,355	26.6	1,500	28.4
46–60	1,222	24.0	1,412	26.7
61–74	1,128	22.1	760	14.4
Marital status				
Married	3,041	59.6	2,591	49.0
Divorced/widowed	347	6.8	648	12.3
Single	1,678	32.9	2,021	38.2
Occupational status				
Working	2,935	57.5	3,029	57.3
Student	742	14.5	843	15.9
Unemployed/searching a job	190	3.7	252	4.8
Retired	909	17.8	604	11.4
Homemaker, male or female	170	3.3	307	5.8
Other	147	2.9	239	4.5
Smoking habits				
Nonsmoker	2,953	57.9	2,895	54.8
Ex-smoker	1,023	20.1	1,120	21.2
Smoker	1,116	21.9	1,264	23.9
Body mass index, kg/m^2				
<20	3,87	7.6	606	11.5
20–<25	2,275	44.6	2,746	51.9
25–30	1,838	36.0	1,360	25.7
>30	570	11.2	546	10.3

[1]Six missing answers for lifetime use of hair coloring products. Numbers in each category may not add up to the total because of missing values.

European population. There were no substantial differences with regard to the sociodemographic characteristics of all the subjects interviewed and those who were randomly selected for patch testing (data not shown).

The percentage of ever-users were higher in Germany (62.9%), The Netherlands (56.6%), and Sweden (55.4%) than in Italy (35.5%) and Portugal (38.4%). The prevalence of ever-use of hair dyes was much higher in women than in men in all countries.

Age distribution showed some variations among different geographic areas, particularly in Sweden, where the proportion of ever hair dye users was higher in the oldest age group (29% vs. 20% in the age group <30 years) and in southern Europe, where the higher proportion of ever hair dye users was observed in those between 31 and 60 years old. Overall, 34.6% of the subjects interviewed (N = 3,583) had used hair coloring products during the last 12 months (190 male [4%], 3,392 female [62%]).

Subjects who had used hair coloring products during the last 12 months were asked to determine the type of product. Altogether. 2,313 of 3,583 individuals (65%) had used oxidation hair coloring products alone or in combination with other techniques, 1,103 individuals (30%) had used exclusively one technique other than oxidation hair coloring products, and 130 (3.6%) individuals had used a combination of techniques other than oxidation hair coloring products.

Overall, 1,503 users (28.4%) of hair coloring products (n = 5,286) had used these products for more than 10 years, 1,080 (20.4%) for 6–10 years, 1,281 (24.2%) for 1–5 years, and 1,290 (24.4%) for <1 year. Among the 2,313 users of oxidation hair coloring products (oxidation only plus oxidation and other techniques), the rate of long-term use was even greater, with 40.8% using the products for more than 10 years, 27.9% for 6–10 years, 23.5% for 1–5 years, and 5.9% for <1 year. The mean duration of use for individuals who colored their hair 10 years or more is 21 years.

Localized itchy skin rash lasting more than 3 days on the scalp and face/ears, during the last month, last year, and lifetime

Ever-hair dye users reported an itchy skin rash on the scalp and/or face/ears more often than nonusers (Table 2). Itchy skin rash on face/ears only was reported by 4.3% of hair dye users and by 2.7% of non-users during the last month; by 6.3% and 3.8%, respectively, during the last year (excluding the last month); and by 10.3% and 5.4%, respectively, during their lifetime (excluding the last year). Inclusion of the site "face/ears" in the absence of scalp involvement in the decision tree contributes to making the attribution of clinical relevance more conservative because the face in particular is the site of contact allergic reactions to many cosmetic and noncosmetic products and of other skin diseases. The lifetime prevalence of itchy skin rash lasting more than 3 days on areas including the scalp was 19.4% in hair dye users versus 9.3% in nonusers ($P < 0.001$).

Confirmed diagnosis of contact dermatitis during the last month, last year, and lifetime

Confirmed contact dermatitis was reported by 0.2% of hair dye users and by 0.1% of nonusers during the last month ($P = 0.388$); by 0.2% in both groups during the last year (excluding the last month) ($P = 0.832$); and by 9.5% and 4.1%, respectively, during their lifetime (excluding the last year) ($P < 0.001$). The characteristics of contact dermatitis (allergic, irritant) are not specified and its site is not related specifically to areas exposed to hair coloring products in consumers.

Lifetime avoidance of hair coloring products because of any skin reaction

Of the total of 10,425 subjects, 624 (6%) reported avoiding hair dyes because of any skin problem during their lifetime. Considering all 5,286 hair dye users, the proportion of subjects with a history of avoidance was 11.7%. Most of them (60%) declared noticing the skin problem while the hair colorant was on the head (before rinsing), 11.4% within 1 hour after rinsing, and 6% within 6 hours. Eighty-three subjects (13.3% of ever-users who reported a skin problem) indicated that the problem began between 6 hours and 3 days after rinsing.

Among the 1,151 exclusive oxidation hair dye users, 114 (9.9%) reported a history of avoidance. Most of these users (61.9%) declared noticing the skin problem while the

Table 2. Prevalence rates of localized itchy skin rash lasting more than 3 days on selected skin areas in ever-users and non-users of hair coloring products

	Not users		Users		
	N = 5,102[1]	%	N = 5,286[1]	%	P-value
Itchy skin rash during last month					
Face/ears only	139	2.7	225	4.3	< 0.001
Scalp only or both face/ears and scalp	98	1.9	180	3.4	< 0.001
Scalp or face/ears	237	4.7	405	7.7	< 0.001
Rash not involving scalp or face/ears	534	10.5	758	14.3	< 0.001
Itchy skin rash during last year (not including last month)					
Face/ears only	194	3.8	332	6.3	< 0.001
Scalp only or both face/ears and scalp	127	2.5	254	4.8	< 0.001
Scalp or face/ears	321	6.3	586	11.1	< 0.001
Rash not involving scalp or face/ears	872	17.1	1,203	22.8	< 0.001
Itchy skin rash during lifetime (not including last year)					
Face/ears only	273	5.4	545	10.3	< 0.001
Scalp only or both face/ears and scalp	204	4.0	479	9.1	< 0.001
Scalp or face/ears	477	9.3	1,024	19.4	< 0.001
Rash not involving scalp or face/ears	1,369	26.8	1,802	34.1	< 0.001

[1]Numbers in each category may not add up to the total because of missing values.

Table 3. Age-standardized prevalence rates of positive patch test reactions to *p*-phenylenediamine

	No. of positive reactions	Total of patch tested[1]	Age-standardized prevalence (95% confidence)
Total	22	2,739	0.8 (0.6–1.0)
Men	10	1,234	0.8 (0.5–1.1)
Women	12	1,499	0.8 (0.5–1.1)
Hair colorant lifetime use			
Yes	12	1,532	0.8 (0.5–1.1)
No	10	1,191	0.8 (0.4–1.2)
Oxidative hair colorant use in the last year			
Yes	3	323	0.9 (0.0–2.0)
No	19	2,400	0.8 (0.5–1.1)
Black henna tattoo lifetime use			
Yes	7	207	3.2 (0.4–6.0)
No	15	2,485	0.6 (0.3–0.9)

[1]Numbers in each category may not add up to the total because of missing values.

product was on the head, 11.9% within 1 hour after rinsing, and 7.2% within 6 hours. Forty-five subjects (14.1% of oxidation hair dye users who reported a skin problem) indicated that the problem began between 6 hours and 3 days after rinsing.

Temporary and permanent tattoos

Of the 10,391 individuals who provided information on temporary tattoos during their lifetime, 927 subjects (8.9%) reported having had a temporary henna tattoo. The color of henna was determined as black by 570 individuals (61.5%) and as red by 305 (32.9%). Among all 10,339 subjects who responded to the question on black henna tattoo, 570 (5.5%) had had black henna tattoos (3.6% of men and 7.2% of women). The prevalence was highest in the youngest age group (18–30 years) both for men and women (58.9% and 54.3% of tattoo users, respectively).

Of the 10,391 subjects who provided information on permanent tattoos during their lifetime, 1,207 (11.6%) reported having a permanent tattoo. Of these subjects, 48% were men and 52% women; 36% were younger individuals (<30 years), 37% were 31–45 years old, 19% were 46–60 years old, and almost 9% were in the older age group (61–74 years).

Patch test results to PPD

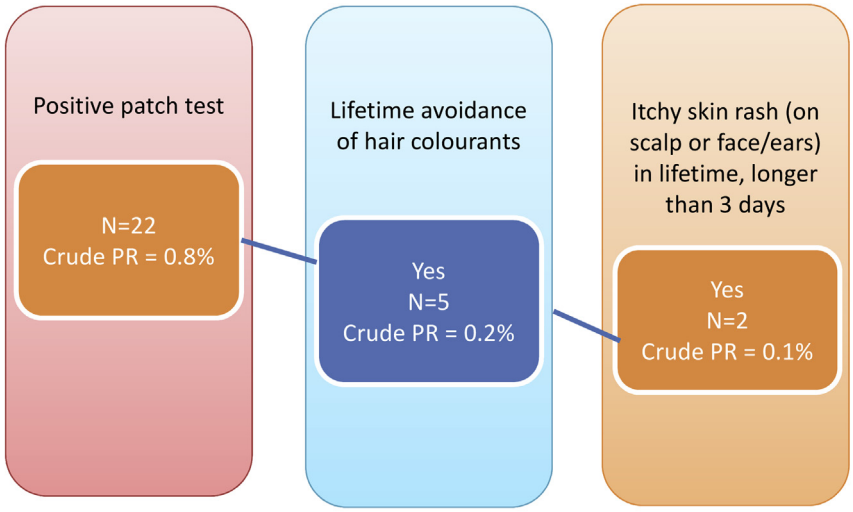
Overall, 22 of 2,739 patch tested subjects were positive to PPD, with a prevalence rate of 0.8%. Altogether, 7 weakly positive (+), 9 strongly positive (++), and 6 extreme (+++) reactions were observed throughout the study. The age-standardized prevalence rates of sensitization to PPD are given in Table 3. The same prevalence rates were observed for men and women and for ever-users of hair coloring products and nonusers (0.8%). The prevalence was 0.7% for all oxidation techniques (exclusive or in combination) and was 0.9% for exclusive oxidation hair dye users in the last year. However, the prevalence rate among black henna tattoo users was 3.2% (95% confidence interval [CI] 0.4–6.0) versus 0.6% (95% CI,0.3–0.9) among nonusers, showing a significant linear trend across the levels of response +, ++. and +++ ($P < 0.0001$ for exact Cochran-Armitage trend test). All subjects who reported use of a red henna tattoo were negative to PPD.

Clinical relevance

Of the 22 positive reactions to PPD, two (both in women) were considered clinically relevant for hair dye exposure according to the algorithm used (Figure 1). The age-standardized prevalence of clinically relevant reactions to PPD was 0.1% (95% CI 0.0–0.2).

Risk factors for PPD contact allergy

The different risk factors for contact allergy to PPD were investigated in terms of odds ratios (ORs) (Table 4). Investigated variables included gender, age, country, present or last occupation, hair dye ever-use, duration of hair dye use, black henna tattoos ever applied, and use of anesthetics in the last 12 months. A strongly significant association was observed between positive reactions to PPD and black henna tattoos use, with a crude OR estimate of 5.79 (95% CI 2.34–14.37), which becomes 9.33 (95% CI 3.45–25.26) in a logistic regression model with adjustment for gender, age, and the other variables. The same significant association with black henna tattoos was observed when the analysis was performed in separated strata of gender, with an OR of 7.95 in men versus 10.86 in women. No significant association with PPD positivity was observed for hair dye ever-use or duration of hair dye use. In addition, no significant linear trend across the levels of duration of hair dye use was detected after adjusting for potential confounders.



All clinically relevant reactions to hair colourants	Total of patch tested	Age-standardized prevalence (95% CI)
2	2,739	0.1 (0.0-0.2)

Figure 1. Clinical relevance of positive patch test reactions to *p*-phenylenediamine in hair coloring products. Algorithm of clinical relevance to contact allergy to PPD in hair coloring products. CI, confidence interval; PR, prevalence rate.

Analysis on additional questionnaire for patch tested subjects

A total of 2,560 of 2,727 subjects patch tested and interviewed using the extended questionnaire were also interviewed with the additional questionnaire.

As expected, the prevalence of a positive patch test reaction to PPD was significantly higher in subjects who had a reaction to hair coloring products in their lifetime (2.8% vs. 0.5% for no reaction, $P = 0.012$), particularly in those whose eyelids and face had swelled after a reaction (14.3% vs. 1.2% for no swelling, $P = 0.033$). The prevalence rate was not significantly different for those who reported lifetime use of hair color versus those who reported no use (0.8% vs. 0.9%). In subjects who had black henna tattoos in their lifetime, the prevalence was substantially higher (3.7% vs. 0.7% for nonusers of temporary black henna tattoos, $P < 0.001$). This finding was confirmed by a significantly higher prevalence in those who had an itchy rash that appeared several days after the application of a black henna tattoo on a tattoo site (45.5% vs. 1.1% for no rash, $P < 0.001$).

DISCUSSION

This is a pan-European population-based study on PPD allergy using patch testing and a standardized questionnaire. The prevalence rate found (0.8%, 95% CI 0.6–1.0) is in the range of rates reported in previous studies in Europe (0–1.5%) (Dotterud and Smith-Sivertsen, 2007; Mortz et al., 2001; Nielsen and Menné, 1992; Nielsen et al., 2001; Schäfer et al., 2001; Seidenari et al., 1990; Thyssen et al., 2009), even though each of those studies was performed out in a single center. The patch test system used, TRUE Test (Mekos, Hillerød, Denmark), has been well standardized for many years. In a comparative study of TRUE Test versus a chamber system, the PPD TRUE test performed equally well compared to the chamber system, eliciting a slightly higher number of positive patch tests (Lazarov et al., 2007).

The clinical relevance of positive patch tests to PPD has not been studied in population-based studies. PPD allergy is generally attributed to hair coloring products through consumer use or occupational exposure of hairdressers to cross-reacting chemicals and to black henna tattoos. In clinical studies, PPD positivity is associated with hair dyeing to various degrees (Schnuch et al., 2008; Søsted et al., 2013; Uter et al., 2014).

Table 4. Risk factors for *p*-phenylenediamine contact allergy

	OR[1] *(95% CI)*	*OR*[2] *(95% CI)*
Sex		
Men	1	1
Women	0.99 (0.43–2.30)	0.85 (0.36–2.01)
Ever hair colorant use		
Nonusers	1	1
Users	0.93 (0.40–2.17)	0.86 (0.30–2.50)
Duration of hair colorant use		
Nonusers	1	1
≤10 years	0.54 (0.18–1.58)	0.57 (0.16–1.97)
>10 years	1.95 (0.74–5.15)	2.19 (0.56–8.62)
Black henna tattoo ever applied		
No	1	1
Yes	5.79 (2.34–14.37)	9.33 (3.45–25.26)

Abbreviations: CI, confidence interval; OR, odds ratio.
[1]Estimates from univariate logistic regression models.
[2]Estimates from multiple logistic regression models including terms for gender and main terms selected by forward stepwise algorithm: age and black henna tattoos ever applied.

An estimation extrapolating clinical data to a population level on PPD that elicited allergic contact dermatitis was performed using Information Network of Departments of Dermatology (IVDK) data on 83,030 patch tested consecutive eczema patients. According to this estimation, 0.11% of patients had PPD allergy related to use of hair coloring products by consumers; 0.11% had PPD allergy related to occupational exposure associated with hair coloring products, paints, or rubber; 0.06% had allergy related to exposure to clothing and shoes; and 0.21% had allergy related to unspecified exposures (Schnuch et al., 2008). Our study confirms the estimation of the rate of PPD allergy related to consumer use of hair coloring products (0.1% of the general population according to our results). Evaluation of the clinical relevance to hair coloring products was performed using an algorithm devised for population-based studies (Rossi et al., 2010).

Our study found no additional risk for PPD contact allergy from the use of hair coloring products on the population level. No difference was found in prevalence rates between lifetime users of hair coloring products and nonusers, and no difference was found between males and females despite more frequent use of hair coloring products among females. No association was found with lifetime use of hair coloring products (OR 0.86, 95% CI 0.30–2.50). No statistically significant association was found with duration of use (OR 0.57, 95% CI 0.16–1.97 for <10 years of use; OR 2.19, 95% CI 0.56–8.62 for >10 years of use). No significant linear trend across the different durations of use was found after adjusting for confounders. However, the sample size of this population-based study might have been too small to detect a significant difference, in contrast to clinical studies in which a higher prevalence is expected.

Nevertheless, there is a clear relationship between reactions to hair coloring products and positive patch test results to PPD. Thus, the prevalence of PPD allergy was significantly higher in subjects who had a reaction to hair coloring products during their lifetime (2.8% vs. 0.5%), particularly among those whose eyelids and face had swelled after a reaction (14.3% vs. 1.2%). Hillen et al. (2007) reported that sensitization to PPD was found to be significantly increased in patients with scalp dermatitis. PPD allergy in hairdressers could not be investigated because there was not a single hairdresser among the PPD-positive subjects (past or present occupation).

Use of black henna tattoos appeared to be a significant risk factor for PPD contact allergy (OR 9.33, 95% CI 3.45–25.26). According to European legislation (Regulation (EC) No1223/2009, EUR, Lex Europa of the European Parliament on cosmetic products, 30 November 2009), the maximum on-head exposure to PPD through finished hair coloring products is limited to 2% . Black henna tattoos may contain even higher concentrations (reaching 64%) (de Groot, 2013). A consumer presensitized by a black henna tattoo will be at higher risk for elicitation of a serious reaction when using a hair coloring product containing PPD (Jacob et al., 2008; Kazandjieva et al., 2007; Marcoux et al., 2002; Redlick and DeKoven, 2007) and potentially cross-reacting colorants. There are more than 100 reports in the literature on sensitization to PPD by black henna tattoos (de Groot, 2013). Severe edematous reactions to hair coloring products leading to hospitalization of or emergency department visits by adolescents sensitized by black henna tattoos have been described (Hink and de Winter, 2006; Jasim et al., 2005; Onder, 2003; Raboobee, 2004; Shavit et al., 2008; Sosted et al., 2006).

Thus, compared to hair dyeing, black henna tattoos appear to be a significant risk factor for PPD allergy (see Table 4) and for severe skin reactions to PPD (Krasteva et al., 2010). This finding is in line with quantitative assessment of the allergy induction threshold for PPD indicating that the high-exposure conditions for black henna tattooing clearly led to values exceeding the induction threshold, whereas maximal hair colorant use exposure to PPD was found to be close to the induction threshold (Goebel et al., 2012). Consequently, a single application of a black henna tattoo is more likely sufficient to induce contact allergy than hair coloring. An estimated mean of 2.5% of individuals using black henna tattoos become sensitized to PPD (de Groot, 2013). Improved education of the public, and especially of younger people, about the risks of black henna tattoos is needed. The relationship between induction and elicitation dose follows general rules of contact sensitization and is not confined to PPD (Friedmann, 2007).

MATERIALS AND METHODS

Study design

The EDEN Hair Color Study is nested within the EDEN Fragrance Study. The study design and data collection methods of the EDEN Fragrance Study were previously published (Naldi et al., 2014; Rossi et al., 2010). Briefly, the study was a descriptive epidemiology survey conducted in several European regions, including the metropolitan areas of Malmö (Sweden), Jena, Thüringen (Germany), Heidelberg, Baden-Württemberg (Germany), and the provinces of Groningen (The Netherlands), Bergamo (Italy), and Coimbra (Portugal). A random sample was selected from the general population, based on electoral precincts, aged 18 to 74 years (Naldi et al., 2014). The study followed a stratified, proportional sampling with replacement design. A total of 10,425 subjects were interviewed with a standardized questionnaire and a specific questionnaire regarding allergy to PPD, and a random sample of 2,739 subjects was patch tested to investigate sensitization to PPD (TRUE Test) (Table 5). Less than 1% of the participants refused to be patch tested. The study was approved by the ethics committee of each

Table 5. Study participants and randomly selected patch tested subjects by country

	Total no. of subjects			Randomly selected patch tested subjects	
Country	Males	Females	Total[1]	Total no. patch tested	Percent patch tested
Germany	1,532	1,861	3,394	876	25.8
Italy	850	1,151	2,003	546	27.3
The Netherlands	629	547	1,179	362	30.7
Portugal	953	1,050	2,003	531	26.5
Sweden	903	906	1,809	424	23.4
Total	4,867	5,515	10,388	2,739	26.4

[1]Thirty-seven missing answers on hair dye use.

participating center, and all participants provided written informed consent.

Patch testing

PPD was tested in accordance with TRUE Test (equivalent to an applied amount of 90 μg PPD cm^2). The patch test procedure and its high standardization have been previously published (Rossi et al., 2010). Patch testing was performed according to the International Contact Dermatitis Research Group (ICDRG) guidelines: weak (+), strong (++), and extreme (+++) reactions with an allergic morphology were considered positive reactions.

Data collection

The interview was conducted face to face with a trained interviewer. The main questionnaire consisted of three parts (Naldi et al., 2014; Rossi et al., 2010). The first part recorded demographic and personal characteristics, and the second part recorded any history of skin problems (Naldi et al., 2014). The interviewees were asked to describe any previous dermatological diagnoses made by a physician or dermatologist, the treatment received, allergy tests performed, and any symptoms present at the time of the interview.

The third part contained questions about exposure to different types of products. The main questionnaire designed for all participants of the EDEN Fragrance Study was extended with specific questions about the use of hair coloring products and black henna tattoos. Subjects who were tested with PPD were interviewed with an additional questionnaire regarding potential occupational exposures to PPD and cross-reacting chemicals and gave more detailed information about clinical reactions. The reliability of answers to the questions about hair colorant and tattoo use was previously assessed in 120 subjects (20 per participating center) by calculating Cohen kappa statistics. An overall good level of agreement was found.

Clinical relevance of PPD contact allergy to hair coloring products

A clinically relevant reaction was defined as follows: positive patch test to PPD (+/++/+++ reactions) in a subject who also reported an itchy skin rash lasting more than 3 days on the scalp and/or face/ears in the last month and/or in the last year and/or during the lifetime, plus a history of avoidance of hair coloring products because of any skin problem or a lifetime history of reactions to these products.

Data analysis

Descriptive information is presented in the tables as numbers with percentages. Continuous variables were categorized by using quartiles or tertiles as cutoff thresholds. Some continuous variables are also presented as mean with standard deviation and 95% CI. Main information is also presented in strata of gender and country of origin. When required, the Fisher exact test was used to compare prevalence rates among different categories. When appropriate, the Cochran-Armitage test was used to test for linear trend across the levels of variables categories.

Prevalence rates of PPD-positive subjects are reported as both crude estimates and age-standardized estimates with 95% CI. Age standardization was performed according to the direct method (Ahmad et al., 2001). European population was taken as reference for standardization. As appropriate in a descriptive survey, measures of association between PPD positive reactions and main variables are expressed as OR with 95% CI. OR estimates were obtained by univariate analysis as well as multivariate analysis by using multiple logistic regression in order to control for potential confounders. A separate analysis of ORs in strata of gender was also performed in the same manner as the main analysis. ORs were considered statistically significant when 1 was not included in the 95% CI. For all statistical tests, $P < 0.05$ was considered significant.

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CONFLICT OF INTEREST

The sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of data; or in the preparation, review, or approval of the manuscript, and decision to submit the manuscript for publication. All authors participated actively in the study. The authors alone are responsible for the content and writing of the paper. Magnus Bruze is a member of REXPAN, an independent expert panel to RIFM.

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